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Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review

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Abstract

Clinical outcomes of patients with diabetes, foot ulceration and peripheral artery disease (PAD) are difficult to predict. The prediction of important clinical outcomes, such as wound healing and major amputation, would be a valuable tool to help guide management and target interventions for limb salvage. Despite the existence of a number of classification tools, no consensus exists as to the most useful bedside tests with which to predict outcome. We here present an updated systematic review from the International Working Group of the Diabetic Foot, comprising 15 studies published between 1980 and 2018 describing almost 6800 patients with diabetes and foot ulceration. Clinical examination findings as well as six non-invasive bedside tests were evaluated for their ability to predict wound healing and amputation. The most useful tests to inform on the probability of healing were skin perfusion pressure ≥40mmHg, toe pressure ≥30mmHg or $TcPO_2$ ≥25mmHg. With these thresholds, all of these tests increased the probability of healing by >25% in at least one study. To predict major amputation, the most useful tests were ankle pressure <50mmHg, ABI <0.5, toe pressure <30mmHg and $TcPO_2$<25mmHg, which increased the probability of major amputation by >25%. These indicative values may be used as a guide when deciding which patients are at highest risk for poor outcomes and should therefore be evaluated for revascularisation at an early stage. However this should always be considered within the wider context of important co-existing factors such as infection, wound characteristics and other comorbidities.

Keywords: peripheral artery disease, diabetes, diabetic foot, foot ulcer, prognosis, amputation

Introduction

The presence of peripheral artery disease (PAD) constitutes a significantly increased risk of failure to heal and major lower limb amputation in persons with diabetes and a foot ulcer (1). PAD is a variable disease in terms of its distribution and severity. It is well recognised that patients with diabetes exhibit a different pattern of peripheral arterial disease compared to those without diabetes (diffuse, distal disease with high prevalence of medial sclerosis and poor collateral formation) (2). Once the diagnosis of PAD is established in these patients (2), the next step should be assessment of the severity of the perfusion deficit. There are a number of validated scoring systems that may be used for classification and prognosis of diabetic foot ulcers and almost all incorporate a component relating to PAD (3). Typically, subjective bedside evaluations (including assessment of pulses or symptoms suggestive of PAD) are combined with non-invasive objective tests that can be used for the assessment of the tissue perfusion deficit to inform the clinician of the healing potential of the ulcer. Different tests are advised and also the extent of the perfusion deficit that should be the threshold for subsequent intervention can be a matter of debate. Therefore, it would be useful to be able to identify any specific characteristics of PAD that may be associated with poor outcomes, in order to help decide whether revascularisation is likely to be successful or futile, regardless of strategy.

The aim of this systematic review is to update our previous review on the performance of non-invasive bedside tests to predict outcomes in diabetic foot ulceration (4), in order to guide the treating clinician as to the likely outcome and help guide management decisions accordingly.

Methods

Search methods

Using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance (5), we updated our previous systematic review (4), guided by a recent consensus document on updating systematic reviews (6) and the IWGDF methodology document (7). As a start, the population of interest (P), interventions (I), comparators (C) and outcomes (O) were defined, and clinical questions (PICOs) were formulated accordingly. These definitions and PICOs were

reviewed for their clinical relevance by the IWGDF Editorial Board and external experts worldwide, from various geographical regions. Final definitions and PICOs are integrated within this paper.

We searched the MEDLINE and EMBASE databases for studies relating to the prognosis of PAD amongst patients with diabetes and foot ulceration, updating the previous search and therefore capturing any new records published between June 2014 and June 2018 (Appendix A). Two reviewers independently screened the abstracts for inclusion and a third reviewer adjudicated any conflicts. The full-text of screened articles was accessed and assessed for inclusion and data were then extracted and verified by members of the IWGDF PAD working group.

Inclusion / exclusion criteria

We included studies that evaluated non-invasive bedside tests in patients with diabetes and foot ulceration to predict clinical outcomes such as clinical symptoms, signs or an objective index measure of PAD. Studies were excluded if they evaluated patients with an intact foot or assessed only demographic factors as predictors of outcomes. The clinical outcomes of interest were wound healing and major amputation.

Investigations of reduced perfusion that were considered included clinical examination, ankle and toe pressures / indices, Doppler waveform analysis, transcutaneous oxygen pressure ($TcPO_2$), laser Doppler imaging, pole test and objective measures of skin temperature. These tests were considered if reported with a cut-off value or threshold to predict outcomes. Gold standard tests used to diagnose PAD included magnetic resonance angiography (MRA), computed tomographic angiography (CTA) and digital subtraction angiography (DSA).

Studies with insufficient information on the revascularisation status of the cohort during follow up were excluded, as were those with <6 months duration of follow up. Studies that did not report data allowing the calculation of sensitivity and specificity (and associated likelihood ratios) were also excluded.

Primary endpoints

The primary endpoints for this review were positive and negative likelihood ratios (PLR and NLR) for healing and major amputation. Likelihood ratios are used to express a change in odds of reaching an outcome, in the context of a known pre-test probability of disease (ie knowledge or estimation of the prevalence of disease in the studied population). The PLR gives the change in odds of experiencing an outcome if the test is positive, whereas the NLR expresses a change in odds of experiencing an outcome if the test is negative.

A PLR or NLR of 1.0 means that the test does not change the probability of the outcome over and above the pre-test probability and therefore is not a useful prognostic test. As a general rule of thumb, a test is considered to have very good performance if PLR ≥10 (representing an increased probability of the specified outcome by around 45% in the presence of a positive test result) and NLR≤0.1 (representing a decrease in the probability of the specified outcome of around 45% in the presence of a negative test result) (8) (9). The higher the PLR, the greater the ability of the test to rule in the outcome of interest, whilst a smaller NLR reflects better ability of the test to rule out the outcome. The practical application of this is to identify the most useful bedside tests that will inform the healthcare professional as to the probability, or not, of the patient experiencing healing or major amputation (Table 1).

Data were analysed as univariable associations of PAD markers with clinical outcome, due to the many factors affecting the likelihood of healing and major amputation. Whilst we recognise the importance of other confounding factors on clinical outcome, we lacked individual patient data from which to adjust our analyses for them.

Data extraction and quality assessment

Data extraction was undertaken and independently verified by two reviewers. Methodological quality was assessed using the Quality in Prognosis Studies (QUIPS) tool. Studies were rated as low quality (0), in which case they were excluded, acceptable (+) or high quality (++). The populations evaluated were heterogeneous, as were the outcomes reported and prognostic tests used, therefore no meta-analysis was undertaken. Instead, measures of test performance were presented for each prognostic test used and summarised

within and across studies. Where not explicitly reported, sensitivity / specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated from the available data and reported in the data table. The median and range of summary statistics, including estimates of predictive performance, are presented, stratified by index test and population studied.

Evidence statements

We drew conclusions for each intervention based on the strength of the available evidence and summarised this as evidence statements with accompanying assessment of the quality of the evidence, according to GRADE (10).

Results

Search results

In the search performed for our previous systematic review 9476 studies were screened (published between 1980-2014), which resulted in total of 11 observational studies reporting data from 5890 patients with diabetes and foot ulcer. Our updated search included papers published between June 2014 and June 2018. Our initial search yielded 9068 titles, of which 3 observational studies (comprising in excess of 900 patients with diabetes) and 1 systematic review / meta-analysis ultimately met the inclusion criteria. Therefore, after including 11 studies from our previous review (4), a total of 15 studies were included in the qualitative data table for this updated review, comprising almost 6800 patients (Table 2). One of these studies was the systematic review of Wang et al. from 2016 that had less stringent inclusion criteria and that had a larger number of studies included compared to the current review. For comparison we included this study (11). A PRISMA flow diagram illustrating the search strategy is included in Figure 1.

Patient demographics

The mean or median age of the cohort studies ranged between 58 and 76 years, whilst the proportion of men was between 57% and 74%. Thirteen studies reported exclusively on patients with diabetic foot ulceration (12), (13) (14) (15) (16) (17) (18) (19) (20) (11) (21) (22) (23) , whereas 2 studies included a mixed

cohort of patients, of which at least 80% of patients had diabetes (24) (25). One study investigated the prognostic performance of PAD measures in patients with foot infection and/or ischaemia (Fontaine III/IV) (24). Severity of ulceration was assessed in 6 studies and the proportion of patients with Wagner grade ≥3 ranged from 16% to 61%. Seven studies did not report on ulcer severity (12) (16,25) (18) (20) (21) (11).

Revascularisation

In those studies reporting it, revascularisation rates ranged from 5% to 100%, with angioplasty (34%) more frequently used than open revascularisation (21%). Four studies excluded patients who underwent revascularisation (14) (16) (18) (23).

Prognostic tests evaluated

Only two studies evaluated the use of clinical examination to predict outcome (24) (13). Ten studies evaluated ABI or ankle pressures (12) (14) (16) (25) (19) (15) (11) (22) (21) (23); other measures of perfusion evaluated were toe brachial index (TBI) or toe pressures (14) (16) (25) (18) (15) , $TcPO_2$ levels (24) (18) (11) (21) (23): , skin perfusion pressure (16) (20), tibial waveform analysis (17) and fluorescein toe slope (25). Two studies provided data on different thresholds of the same investigation (18) (15) and 8 compared data on the performance of multiple modalities (14) (16) (25) (18) (15) (11,23) (24) (21), allowing direct comparison within the same cohorts.

Clinical outcomes

Table 3 presents clinical outcomes by study. The rate of primary healing varied between 36% and 83%, whilst the rate of major amputation ranged between 3.6% and 35%. The highest rate of major amputation (35%) was reported by Tsai *et al*, who evaluated a high-risk population of patients with diabetic foot ulcer and dialysis-dependent end-stage renal failure (17) .

PICO: In a person with diabetes, foot ulceration and PAD, which clinical signs, symptoms or non-invasive bedside tests may predict wound healing and major amputation?

Non-invasive tests to predict wound healing

Clinical signs or symptoms

Two studies evaluated clinical signs or symptoms of PAD as possible predictors of clinical outcome (13) (24). Bunt *et al* conducted a cohort study that evaluated the predictive value for healing of palpable pedal pulses and $TcP0_2$ in 147 patients (90% of whom had diabetes) with a foot infection or ischaemia, treated with the same management protocol in a secondary care setting, (24) . Healing was defined as primary healing or healing after minor amputation or debridement, with or without revascularisation. All 44 patients with readily palpable pulses healed without revascularisation, suggesting that palpable pulses could be a strong predictor of healing. In the 103 patients with reduced or no pulses the $TcPO_2$ was measured, and those patients with $TcP0_2$ <30 all underwent revascularisation (46%). The presence of palpable pedal pulses in the whole cohort was associated with higher likelihood of healing (RR 2.26, 95% CI 2.05-2.49; sensitivity 35%, specificity 100%). The NLR was 0.65, which corresponds to little change in the probability of healing if pulses are absent. All patients with palpable pedal pulses healed. It should be noted that the risk of bias in this one study on the presence of palpable pulses is unclear due to lack of many details.

Elgzyri *et al* undertook a prospective cohort study of 478 people with DFU who had toe pressure <45mmHg or ankle pressure <80mmHg (13) who underwent revascularisation (66% endovascular, 34% open surgery). The primary focus of the paper was time to revascularisation, and they reported that patients who underwent revascularisation within 8 weeks of referral were more likely to heal (HR 1.96; 95% CI, 1.52-2.52, p<0.001). In addition, those with intermittent claudication appeared to have an increased likelihood of healing (HR 1.64; 95% CI, .26-2.13; p<0.001). No explanation for this finding was given, however, the presence of intermittent claudication does not appear to be a useful prognostic

measure given a PLR of 1.59 and a NLR of 0.81. A limitation of this study is that the tests were performed in patients with the most severe ischaemia.

Neither of the two aforementioned studies compared clinical examination against objective measures of perfusion, hence their accuracy in detecting ischemia is unknown.

Ankle pressure or ankle brachial index

In studies evaluating ankle pressure, using a threshold of >50mmHg produced a PLR for wound healing between 1.08 and 1.46, meaning that there is almost no improvement on the probability of healing when the ankle pressure is above this threshold. Increasing the threshold to ≥70 or ≥80mmHg improved the PLR to 2.52-3.24, which represents a minor increase in the probability of healing. However, in one study, using a value of ≥70mmHg achieved an NLR of 0.1, suggesting that the chance of *not* healing was increased if the ankle pressure was below 70mmHg (25). Four studies that evaluated ABI (normal defined as threshold ≥0.8, ≥0.9 or between 0.9 and1.3,) yielded variable results (19) (11) (21) (22). The ABI was not strongly predictive of healing (PLR 1.0-3.09; NLR 0.29-1.0) in two studies (19) (22) as well as in the systematic review of Wang et al (11), with poor ability to rule in or rule out the outcomes of interest as reflected by the low magnitude of the PLR and NLR (PLR range 1.0-3.09; NLR range 0.29-1.0). However, a third study of 564 patients with Wagner grade II or III ulcers found ABI >0.9 strongly predictive of healing (PLR 13.83) but with a trade-off for a poor NLR (0.6), i.e. the ABI could not predict well who did not heal (23).

Toe pressure

The use of toe pressure to predict healing was examined at thresholds of ≥30mmHg in four papers (14) (16) (18) (15) , with a PLR between 1.12 and 5.00; the NLR was between 0.28 and 0.88. When the threshold was increased to ≥45mmHg (18) (15), there was little difference in the magnitude of the PLR (PLR 2.88 and 4.30).

Skin perfusion pressure

A threshold skin perfusion pressure of ≥40mmHg was associated with moderately good performance for prediction of healing in two studies (PLR 4.86 and 6.40, with NLRs of 0.03-0.40) (20) (16).

Transcutaneous oxygen pressure

At a threshold of 22.5-30mmHg, $TcPO_2$ was shown to have a moderate performance for prediction of healing in three studies (PLR 10.63, 4, and 1.21 NLR 0.16, 0.33 and <0.1) (18) (23) (21). The systematic review of Wang reported a pooled PLR of 5.14 and a NLR of 0.33 using a TcPO2 cut-off < 30 mmHg (11).

Fluorescein toe slope

Fluorescein angiography may be used as a marker of tissue perfusion, as the distribution of fluorescence in the skin after intravenous administration of fluorescein is related to the distribution of blood flow. One study evaluating the use of fluorescein toe slope in comparison with ankle pressure >70mmHg or toe pressure >20mmHg (25) found a similar performance when comparing the three tests. For a toe slope of <18 units, the PLR was 2.47 and NLR was 0.09. This means that it only has a minor ability to predict healing but may be useful to indicate those that will not heal.

Non-invasive tests to predict major lower limb amputation

Eight studies (including the systematic review of Wang et al) evaluated non-invasive bedside tests for the prediction of major amputation (amputation of the leg proximal to the ankle), Table 5 (25) (19) (15) (17) (11) (21) (22) (23).

Ankle pressure or ankle brachial index

Two studies evaluated ankle pressures as predictors of major amputation (amputation of the leg proximal to the ankle) (25) (15). In one study, ankle pressures of <50mmHg and <80mmHg were compared within the same cohort. When the lower threshold was used, there was increased specificity (84% vs 79%) but this was at the cost of reduced sensitivity (20% vs 39%). The higher threshold of <80mmHg performed slightly better (PLR 1.89 vs 1.25; NLR 0.77 vs 0.95) (15) with regards to the prediction of major amputation. Another study used a cut-off

value of <70mmHg, which gave an improved performance with a PLR of 4.28, which corresponds with an increase in the likelihood of major amputation of >25% (25).

One study evaluated ankle brachial index (ABI) as a predictor of major amputation and concluded that a threshold of ABI <0.6 performed best, with a PLR of 68 corresponding to a very high increased probability of major amputation. The NLR was 0.32. This prospective study was performed in a cohort of 564 patients in India with diabetic foot ulceration of which only 15% had PAD (defined as ABI <0.9 or $TcP0_2$<40) (23). In the systematic review of Wang et al (11) a threshold <0.8 was used, which yielded a relatively small change in the probability of limb amputation (PLR 1.93-3.5; NLR 0.39-0.66).

When in one study the combination of an ankle pressure <50mmHg or an ABI <0.5 was evaluated, this was shown to have strong ability to both rule in and rule out major amputation in a further study (19), with a PLR of 8.24, representing a 40% increased probability of amputation, and with a NLR of 0.14.

Toe pressure

A study by Gershater *et al* compared toe pressure thresholds of <30mmHg and <45mmHg and found them broadly equivalent in predicting major amputation (PLR 2.64 and 2.05) (15). When this threshold was reduced to <20mmHg in a different study (25), the PLR was improved to 3.18, which increases the probability of amputation by around 15-20%, but with a corresponding NLR of 0.49, reflecting poor ability to rule out major amputation.

Transcutaneous oxygen pressure

In the two studies on $TcPO_2$, a value < 22.5- 25 mmHg had a PLR of 3.41 and >10, with a NLR of 0.51 and 0.25 (21) (23). In the systematic review of Wang et al, the pooled PLR and NLR were 1.79 and 0.43, respectively (11).

Fluorescein toe slope

In a study of 83 patients with foot ulcers, fluorescein toe slope (the rate of fluorescence on the hallux during the first 10 seconds of its appearance on the toe) <18 unit was found to have a reasonable prognostic accuracy (PLR 4.04, NLR

0.49), which corresponds to an increase in likelihood of major amputation of around 25% (25). This was comparable to the use of ankle pressure (<70mmHg) and toe pressure (<20mmHg) in the same study.

Doppler waveform analysis

One study evaluated the use of Doppler waveform analysis and found that the absence of flow or monophasic signal in the below-knee vessels modestly increased the probability of amputation (PLR 2.18) (17). This was less informative than other tests such as fluorescein toe slope <18 units, toe pressure <20mmHg and combined ABI <0.9 and ankle pressure <50mmHg.

Evidence statement: The following tests increased the probability of healing of a diabetic foot ulcer by >25% in at least one study: a toe pressure ≥30mmHg, a $TcPO_2$ ≥ 22.5-25 mmHg and a skin perfusion pressure ≥40mmHg,

Quality of evidence: Moderate, not all studies obtained consisted results

Evidence statement: The following tests increased in at least one study the probability of a major amputation in a patient with a diabetic foot ulcer by >25%: ankle pressure <70mmHg, ABI <0.6, $TcPO_2$< 25mmHg and a fluorescein toe slope <18 units. The combination of ABI <0.5 and ankle pressure <50mmHg improved this to around 40% in one study.

Quality of the evidence: Moderate, not all studies obtained consistent results

Discussion

This updated systematic review evaluates the performance of six non-invasive prognostic bedside tests (in addition to common clinical examination findings) to predict the likelihood of wound healing or major amputation in patients with diabetes and foot ulceration. Whilst we know that the presence of PAD increases the risk of poor outcomes in a patient with foot ulceration, only a subset of patients will experience them. Although major advances have been made in treating PAD in patients with DFU, both endovascular and open surgical revascularisation

procedures are not without risk. A prognostic test that assesses the severity of the perfusion deficit whilst also informing healthcare professionals (and patients) about the probability of a specified clinical outcome (such as healing or major amputation) would be a useful tool in clinical decision making. It is often not feasible, or necessary, to perform vascular imaging on every patient with a foot ulcer and diabetes when they first present. However, it would be useful for the treating clinician to identify those patients with a higher probability of healing without revascularisation, in order to pursue a conservative approach in the first instance. Similarly, if a patient is identified as having an unacceptably high probability of major amputation, urgent investigation and revascularisation should be considered.

The data reviewed here were heterogeneous, as were the patient cohorts, with probably important differences in wound and patient characteristics, and it is not surprising that no single test performed consistently well across these studies. The presence of palpable foot pulses was associated with future healing in one study but this report was difficult to interpret and the absence of foot pulses does not necessarily mean that an ulcer will not heal, stressing the importance of non-invasive tests. The most useful tests to inform on the probability of healing were skin perfusion pressure ≥40mmHg, toe pressure ≥30mmHg or $TcPO_2$ ≥25mmHg. With these thresholds, all of these tests increased the probability of healing by >25% in at least one study. When such results are obtained, it would be reasonable to undertake an initial period of conservative management, particularly if the patient has a relatively high pre-test probability of healing (e.g. a superficial wound with no evidence of infection).

Although sometimes thought to be the reverse of each other, wound healing and major amputation are different outcomes and can have different determinants. When considering tests to predict major amputation, the most useful were ankle pressure <50mmHg, ABI <0.5, toe pressure <30mmHg and $TcPO_2$<25mmHg. In addition, fluorescein toe slope <18 units performed to a similar standard. Again, all of these tests increased the probability of major amputation by around 25% in at least one study, and the combination of ABI <0.5 and ankle pressure <50mmHg

improved this to around 40%. Therefore, patients in whom these criteria are met could be considered at higher risk of limb loss when compared to those with a less severe perfusion deficit. These patients should be considered for urgent vascular imaging and revascularisation at an early stage of the clinical management of their DFU. However, the use of ABI and ankle pressures in this cohort should be interpreted with a degree of caution. It is well recognised that patients with a supra-normal ABI are at increased risk of mortality, and that a high ABI represents incompressible arteries rather than high intraluminal pressure (26) (27) (28). It is estimated that 30-40% of patients with diabetes have significant medial artery calcification (29) (30) which leads to incompressible vessels and abnormally high ABI. Only some of the studies assessing ABI or ankle pressures excluded patients with abnormally high readings suggestive of incompressible vessels. For example, the systematic review by Wang *et al* defined abnormal ABI as <0.8, whereas Bunt and colleagues recognised ABI >1.3, closing pressure >200 mmHg or incompressible vessels to be abnormal and a sign of mediasclerosis (11). However, the important finding of our review was that low ABI or ankle pressure were useful to predict the likelihood of amputation, but normal results were not useful when predicting the likelihood of wound healing.

The use of a major amputation as an endpoint has certain limitations, as it is a procedure and not an endpoint in the strict sense. The reason for the procedure is rarely indicated – for example, it may be required for sepsis control in a patient in whom revascularisation has been successful, or conversely for a patient with minor tissue loss but intractable pain due to unsuccessful revascularisation or no-option ischaemia. Treatment methods and technologies have changed substantially since 1980, and there is now in our experience a greater propensity to perform minor amputation following revascularisation (including multiple attempts) rather than primary major amputation. In addition, patients included in a prospective study frequently already have a history of prior foot disease, it is therefore impossible to determine where in the disease process an individual patient is and frequently there is no information whether an intervention prior inclusion in a study has been performed. Finally, the occurrence of outcomes such

as wound healing and major amputation can be affected by the duration of follow up, which varied between studies.

In patients with diabetes, PAD and foot ulceration, impaired perfusion is usually only one of the factors contributing to the risk of non-healing and amputation, and the outcome of the ulcer does not rely simply on improving foot perfusion. For instance, in patients who had a lower extremity bypass because of critical limb ischemia (59% had diabetes), more than half of the major amputations during follow-up were performed in patients with a patent bypass. (31). There is clearly a need for further understanding of the contribution of perfusion deficit to the prognosis of patients with a diabetic foot ulcer and the interaction with other local and systemic factors. Bedside tests of perfusion should not be used in isolation and most guidelines have moved toward multi-factorial tools to assess prognosis, which also include other important contributing factors such as infection and wound characteristics. Any prognostic test of PAD severity described in this review should therefore be combined with the evaluation of infection and wound characteristics in order to provide a more meaningful measure of prognosis that encompasses all of the relevant components of DFU. These systems, such as the WIFi classification, require each domain to be graded according to severity, allowing an overall risk category to be calculated as addressed elsewhere in this issue (3). In addition, it is recognised that the combination of more than one test (ie serial testing) may provide more useful information on the likely prognosis than a single test or tests used in isolation (parallel test). However this approach was not reported amongst the majority of the studies included here and this lack of information is a weakness of our review.

Nevertheless, knowledge of the performance of non-invasive bedside tests to predict outcome allows a better understanding of the potential for wound healing or the probability of major amputation, and remains a valuable tool for healthcare professionals involved in the management of patients with diabetes and foot ulceration. However relevant data are limited, heterogeneous and studies are often of relatively poor quality. In order to address this, more effort is required to produce well-designed studies, to use standardised data sets and to develop

international registries, which will more accurately inform on the factors most strongly predictive of poor outcomes. Although developed as guidance for intervention studies, standards of reporting in this area were formulated by a joint team of the IWGDF and European Wound Management Association, which future researchers can use as starting point (32).

Conclusions

Amongst the 15 studies included in this review, comprising almost 6800 patients with a diabetic foot ulcer, the presence of severe perfusion deficit (ankle pressure <50mmHg, ABI <0.5, toe pressure <30mmHg and $TcPO_2$<25mmHg) was associated with >25% increased risk of major amputation, whilst a better perfused foot (skin perfusion pressure ≥40mmHg, toe pressure ≥30mmHg or $TcPO_2$ ≥25mmHg) was found to be more likely to heal. These measures of PAD may be used as a guide when deciding management of patients, and the likelihood of healing or major amputation can be incorporated into the decision to pursue conservative management or a further vascular assessment potentially leading to revascularisation. However, these measures should be used in the wider context, acknowledging the contribution of other clinical predictors of the outcome of a foot ulcer. Further research is required to more accurately evaluate the role of bedside tests of PAD in the prognosis of patients with diabetes and foot ulceration.

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Conflict of interest statements

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All individual conflict of interest statement of authors of this guideline can be found at: https://iwgdfguidelines.org/about-iwgdf-guidelines/biographies/

Author contributions: RachaelF performed the literature search, screened the titles, abstracts and full papers, assessed the literature, extracted data, drew conclusions for the PICOs, completed the evidence tables, and wrote the manuscript. JA checked the evidence table and reviewed the manuscript. EB assessed the literature, extracted data, checked and revised the evidence tables, reviewed and critically revised the manuscript. RobertF screened the abstracts, assessed the literature, extracted data, checked and revised the evidence tables, and reviewed the manuscript. JPH checked the evidence tables and reviewed the manuscript. KK checked the evidence tables and reviewed the manuscript. JLM extracted data, checked the evidence tables and reviewed the manuscript. SN checked the evidence tables and reviewed the manuscript. JR checked the evidence tables and reviewed the manuscript. MV checked the evidence tables and reviewed the manuscript. REZ extracted data, checked the evidence tables and reviewed the manuscript. NCS assessed the literature, drew conclusions for the PICOs, checked and revised the evidence tables, reviewed and critically revised the manuscript. RJH reviewed and provided final consensus for the data extraction, drew conclusions for the PICOs, reviewed and critically revised the manuscript. RachaelF acted as secretary of the working group, RJH as chair of the working group. All authors take full responsibility for the content of the publication.

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Figure 1: PRISMA Flow Diagram

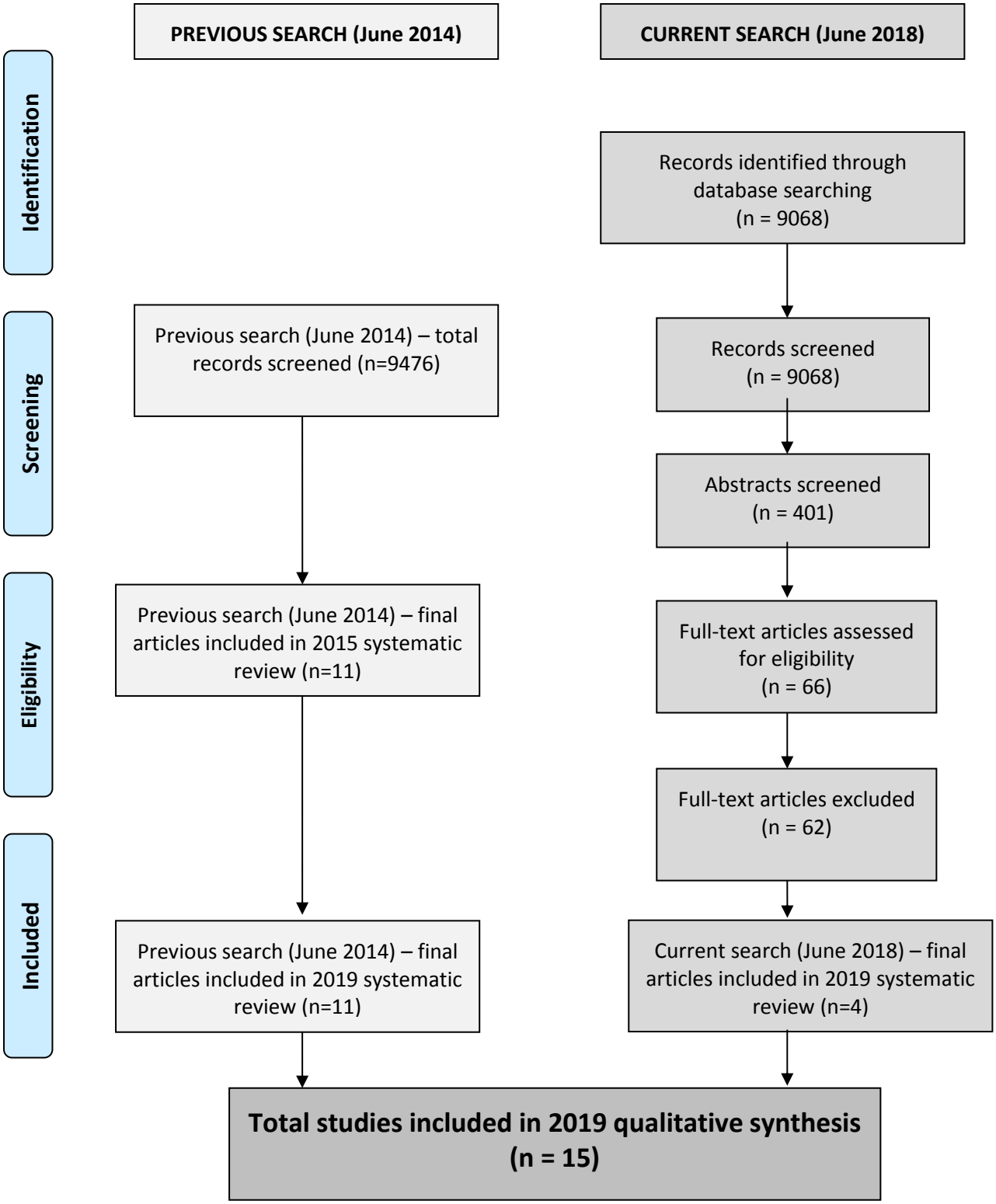

Table 1: Interpretation of likelihood ratios and their effect on probability of disease (34)

High likelihood ratios	Low likelihood ratios	Interpretation – affect on ability to rule in / rule out disease
>10	<0.1	Large
5-10	0.1-0.2	Moderate
2-5	0.2-0.5	Small
1	1	No change

Table 2: Evidence table of all papers included in systematic review

Reference	Study design & setting	Population (age, sex, comorbidity, number [proportion] with DM)	Ulcer characteristics & revascularisation data	Diabetic foot ulcer outcome definition	Relative risk of the outcome (95% CI) for index measurement of PAD	Test performance characteristics for the outcome (sensitivity, specificity, PLR, NLR)	Quality assessment	Comment/ opinion
Apelqvist 2011 (12)	Prospective cohort study Secondary care Median follow up 2 years (range 0.5-2.0)	1151 DFU with toe pressure <45 mmHg OR ankle pressure < 80 mmHg OR non-palpable foot pulses (with Wagner 4-5 OR rest pain); mean age 75 (range 40-92); 61% male; median HbA1c 7.6 (range 3.6-16.0); 69% on insulin therapy	Ulcer severity not reported 505 (44%) underwent revascularization (angioplasty OR surgery)	Healing (primary healing without major OR minor amputation)	Measurable ankle pressure (compressible arteries): 1.12 (0.80-1.55)	Sensitivity 91%; specificity 10%; PLR 1.02; NLR 0.86	++	Analysis by patient 801 (70%) underwent angiography of whom 63% underwent revascularization (39% PTA 39% and 24% surgery).

Elgzyri 2014 (13)	Prospective cohort study Secondary care Median follow up 10 months (IQR 5-16)	478 DFU with systolic toe pressure <45 mmHg OR ankle pressure <80mmHg; median age 74 (IQR 66-80); 60% male; median HbA1c 7.8 (IQR 6.2-9.0); median duration DM 15 years (IQR 10-24)	21% Wagner ≥3 All patients were revascularized: 315 (66%) PTA, 163 (34%) surgery	Healing (primary healing OR healing after a minor amputation)	Intermittent claudication:1.25 (1.16-1.36)	Sensitivity 39%, specificity 75%, PLR 1.59; NLR 0.81	++	Analysis by patient Toe pressure <45 mmHg in 78%; ankle pressure <80 mmHg in 43%
Elgzyri 2013 (14)	Prospective cohort study Secondary care Median follow up 7.5 months	602 DFU with toe pressure <45 mmHg OR ankle pressure < 80 mmHg; median age 76 (range 36-95); 60% male; median HbA1c 7.4 (range 3.6-15.0); median duration	During follow-up 53% of patients were Wagner grade ≥3 No patient underwent revascularization	Healing (primary healing OR healing after minor amputation)	Ankle pressure >50 mmHg: 1.60 (1.04-2.47) Toe pressure >30 mmHg: 1.13 (0.96-1.33)	Sensitivity 93%; specificity 14%; PLR 1.08; NLR 0.48 Sensitivity 55%; specificity 51%; PLR 1.12; NLR 0.88	+	Analysis by patient 42% of patients had no claudication or rest pain

	(range 0-69)	DM 15 years (range 0-61)						
Gershater 2008 (15)	Prospective cohort study Secondary care Duration of follow-up not reported	2511 DFU; mean age 68±15; 59% male; median duration DM 16 years (range 0-70); T1DM 18%; T2DM 82%; insulin 62%	10% Wagner grade 3; 6% Wagner grade 4-5 8% previous vascular surgery; revascularization rates during follow-up not reported	Primary healing (intact skin for 6 months OR at time of death) Major amputation (amputation above the ankle)	Ankle pressure ≥80mmHg: 2.67 (2.41-2.97) Ankle pressure ≥50mmHg: 3.31 (2.71-4.05) Toe pressure ≥45mmHg: 2.86 (2.62-3.12) Toe pressure ≥30mmHg: 1.85 (1.61-2.14) Ankle pressure <80mmHg: 2.26 (1.71-2.97) Ankle pressure <50mmHg: 1.29 (0.92-1.80)	Sensitivity 84%; specificity 67%; PLR 2.52; NLR 0.24 Sensitivity 95%; specificity 35%; PLR 1.46; NLR 0.15 Sensitivity 80%; specificity 81%; PLR 4.30; NLR 0.25 Sensitivity 90%; specificity 30%; PLR 1.28; NLR 0.33 Sensitivity 39%; specificity 79%; PLR 1.89; NLR 0.77 Sensitivity 20%; specificity 84%; PLR 1.25; NLR 0.95	+	Analysis by patient Of patients with rest pain (n=664), 44% healed without any amputation In multiple regression analysis, primary healing was related to the extent of PAD in the whole cohort but not among purely neuropathic ulcers. Amputation among patients with neuroischemic ulcers was also related to extent of PAD after controlling for other factors.

					Toe pressure <45mmHg: 2.98 (2.28-3.91) Toe pressure <30mmHg: 3.24 (2.48-4.24)	Sensitivity 55%; specificity 73%; PLR 2.05; NLR 0.62 Sensitivity 40%; specificity 85%; PLR 2.64; NLR 0.71		
Bunt 1996 (24)	Prospective cohort study Secondary care 2-year study period; follow-up duration not reported	147 patients; 90% DM	All had pedal wound sepsis or Fontaine III/IV ischemia 46% underwent revascularization	Healing (primary healing or healing after a minor amputation/ debridement procedure)	Palpable pedal pulses: 2.26 (2.05-2.49) Diminished/ absent pedal pulses and $TcPO_2$ >30: 1.69 (1.08-2.64)	Sensitivity 35%, specificity 100%; PLR N/A; NLR 0.65 Sensitivity 87%; specificity 46%, PLR 1.60; NLR 0.29	+	Analysis by patient Only those with diminished/ absent pedal pulses underwent $TcPO_2$ measurement (n=103) 90 patients had diminished/ absent pedal pulses and $TcPO_2$ <30 mmHg of whom 68 were revascularized.

Holstein 1980 (16)	Cohort study Secondary care Median time to healing 6.2 months (range 1-23); follow-up duration not reported	32 DFU; 11 on insulin therapy; mean age 68 years	No ulcer characteristics reported Patients undergoing revascularization excluded	Healing (no definition provided)	Toe pressure ≥ 30 mmHg: 2.43 (1.62-3.64) Ankle pressure ≥ 100 mmHg: 2.00 (2.00-2.00) Skin perfusion pressure ≥ 40 mmHg: 1.88 (1.48-2.39)	Sensitivity 72%; Specificity 100%; PLR N/A; NLR 0.28 Sensitivity 60%; Specificity 100%; PLR N/A; NLR 0.40 Sensitivity 64%; Specificity 90%; PLR 6.40; NLR 0.40	+	Analysis by patient Inclusion criteria specified patients with at least 1 month duration of ulceration, i.e, those with early healing or major amputation were excluded
Wallin 1989 (25)	Cohort study Secondary care	83 patients (68 DM) with ulceration or gangrene; mean age 70	Ulcer severity not reported Revascularization performed in 4 patients	Healing (no definition provided)	Ankle pressure ≥70 mmHg: 5.17 (2.08-12.89)	Ankle pressure ≥ 70 mmHg: Sensitivity 93%; Specificity 71%; PLR 3.24; NLR 0.10 Toe pressure ≥20 mmHg: Sensitivity	+	Analysis by limb The ankle pressure in combination with the toe slope improved prognostic accuracy relative to

	Duration of follow-up time not reported			Major amputation (no definition provided)	Toe pressure ≥20 mmHg: 2.65 (1.41-4.97) Fluorescein toe slope ≥18 units: 6.40 (2.16-18.98) Ankle pressure <70 mmHg: 4.53 (2.22-9.26) Toe pressure <20 mmHg: 3.48 (1.65-7.32) Fluorescein toe slope <18 units: 3.69 (1.99-6.86)	86%; Specificity 65%; PLR 2.47; NLR 0.21 Fluorescein toe slope ≥18 units: Sensitivity 95%; Specificity 62%; PLR 2.47; NLR 0.09 Ankle pressure < 70 mmHg: Sensitivity 65%; Specificity 85%; PLR 4.28; NLR 0.41 Toe pressure < 20 mmHg: Sensitivity 60%; Specificity 81%; PLR 3.18; NLR 0.49 Fluorescein toe slope <18 units: Sensitivity 58%; Specificity 86%; PLR 4.04; NLR 0.49		other predictor variables alone or in combination Analysis by limb

Tsai 2013 (17)	Retrospective cohort study Secondary care Duration of follow-up time not reported	97 DFU and dialysis dependence; mean age 65 ± 13 years; 55% male; mean duration DM 18 ± 10; mean HbA1c 7.8 ± 1.6	38% Wagner 3; 23% Wagner 4-5 30% underwent revascularisation	Major amputation	Poor monophasic waveform or absence of flow in below knee vessels: OR 7.61 (P=0.008)	Sensitivity 88%; specificity 60%; PLR 2.18; NLR 0.20	+	Analysis by patient Poor monophasic waveforms or an absence of flow was detected in 83% of dialysis patients with ABI ≤0.90. This waveform criterion also identified 50% of individuals with ABI >1.40.
Kalani 1999 (18)	Prospective cohort study Secondary care 12-month follow-	50 DFU; 74% male; mean age 61±12; DM duration 26 ±14 years; PAD (defined as toe/arm pressure index <0.6) in 64%; 1 patient with previous bypass.	Severity of ulcers not reported No revascularization procedure as all patients were ineligible for angioplasty/ surgery on basis of extensive distal disease and/ or	Healing (intact skin)	$TcPO_2$ ≥25 (no data provided for risk ratio) Toe pressure ≥30 (no data provided for risk ratio) Toe pressure ≥45 (no data provided for risk ratio)	Sensitivity 85%; specificity 92%; PLR 10.63; NLR 0.16 Sensitivity 15%; specificity 97%; PLR 5.00; NLR 0.88 Sensitivity 46%; specificity 84%; PLR 2.88; NLR 0.64	+	Analysis by patient Systolic ankle blood pressure difficult to measure in 22%

	up duration		increased operative risk					
Brechow 2013 (19)	Prospective cohort study of hospitalized patients Secondary care 2-year follow-up duration	678 DFU; mean age 64±11; diabetes duration 15±10; HbA1c 7.9±3.5	51% Wagner ≥3 445 patients underwent angioplasty; 126 underwent arterial reconstruction	Healing prior to discharge Major amputation	ABI >0.9 and <1.3: 2.02 (1.40-2.91) ABI<0.5 or ankle pressure <50mmHg: 25.00 (13.85-41.92)	Sensitivity 12%; specificity 95%; PLR 2.61; NLR 0.92 Sensitivity 87%; specificity 89%; PLR 8.24; NLR 0.14	+	Analyses by patient Patients with MI/ stroke in preceding 6 months, ESRD or active cancer excluded 30% of patients with non-compressible vessels/ ABI>1.3/ ankle pressure >200mmHg included in analyses
Faris 1985 (20)	Cohort study Secondary care	61 DM with ulceration (n=35) or gangrene (n=26); median age 72 years (range 38-86); median	Ulcer severity not reported 28% underwent surgical revascularization	Healing (primary or after minor/ major amputation or after	Skin perfusion pressure ≥40mmHg (unable to calculate RR)	Sensitivity 64%; specificity 17%; PLR 4.86 NLR 0.03	+	Analysis by limb Incompressible arteries found in 5 patients

	Follow-up duration not reported	duration DM 10 years (range 0.5-40)		revascularization)				Technical difficulty measuring toe pressures in 8 patients
Wang 2016* (11)	Systematic review / meta-analysis of clinical trials or observational studies	All patients had DFU. ABI: 20 studies evaluating 2376 patients. $TcPO_2$: 25 studies evaluating 3789 patients. Thresholds: ABI <0.8; $TcPO_2$ 30mmHg.	Variably reported	Complete ulcer healing Limb amputation (no definition provided).		ABI $\geq$0.8: Complete ulcer healing: sensitivity 0.48 (95% CI 0.36-0.61); specificity 0.52 (95% CI 0.42-0.63); DOR 1.02 (95% CI 0.40-2.65). ABI<0.8: Limb amputation: sensitivity 0.52 (95% CI 0.49-0.54); specificity 0.73 (95% CI 0.63-0.81); DOR 2.89 (95% CI 1.65-5.05). $TcPO_2$ $\geq$30mmHg: Complete ulcer healing: sensitivity	Overall: medium risk of bias but low quality evidence	$TcPO_2$ better discriminatory performance to predict complete healing and limb amputation than ABI. Other parameters were reported in this systematic review but not included here as data not able to be pooled.

						0.72 (95% CI 0.61-0.81); specificity 0.86 (95% CI 0.68-0.95); DOR 15.81 (95% CI 3.36-74.45). $TcPO_2$ <30mmHg: Limb amputation: sensitivity 0.75 (95% CI 0.73-0.77); specificity 0.58 (95% CI 0.52-0.64); DOR 4.14 (95% CI 2.98-5.76).		
Fagher 2018 (21)	Retrospective review of prospectively kept database. Secondary care –	236 patients with DFU. Mean age 76 (69-82), 69.9% male. CAD 65.3%, smoking 26.2%	No information on ulcer severity. 16.1% revascularisation during follow up.	Healing within 3 months Major amputation	$TcPO_2$ > 25mmHg: 2.88 (1.43-5.85) $TcPO_2$ < 25mmHg: 5.75 (2.06 – 16.03)	Sensitivity 0.92, specificity 0.23; PLR 1.21, NLR 0.33 Sensitivity 0.58, specificity 0.83; PLR 3.41, NLR 0.51		Short follow-up for ulcer healing and amputation occurrence (12 weeks) Main outcome of the analysis was survival in relation to vascular measurements

	hospital in Sweden. 1 year follow up.							ABI: Proportion who healed were provided for ABI categories but the number in each category not provided
Jeon 2017 (22)	Retrospective review of patient records. Secondary care hospital in Republic of Korea. Follow up duratio	137 patients with DFU. Mean age 61 (SD 12.8), 57.7% male.	39.4% had Wagner III and IV ulcers.	Healing (during an unspecified time period) Any amputation (minor 62 in and major in 5)	ABI ≥ 0.9 Odds ratio 9.07 (3·88, 22·6) ABI < 0.9 Odds ratio 9.01 (3.8, 21.8)	Sensitivity 0.80, specificity 0.69, PLR 2.58, NLR 0.29 Sensitivity 0.69, specificity 0.80, PLR 3.45, NLR 0.39		The analysis compared the ability of 5 different ulcer classification systems to predict amputation. All systems had an AUROC > 0.8 ABI data missing in 28 patients

	n not specified							
Rajagopalan 2018 (23)	Single-centre prospective non-randomized observational study	564 diabetic patients with Wagner II and III foot ulcers Mean age 58.23±10.11 years 380/564=67.4% Men	All diabetic patients with Wagner II and III foot ulcers (no breakdown given) Patients who had revascularisation were excluded	Healing Major amputation	ABI <0.9 Odds ratio (95% CI) for healing 3.5 (2.2,5.7) $TcPO_2$ <40 Odds ratio for healing 0.733 (0.63,0.84) ABI < 0.90 Odds ratio for amputation 0.51 (0.12,0.22) $TcPO_2$ <40 Odds ratio for amputation 2.99 (2.10,4.25)ing 0.733 (0.63,0.84)	From ROC curves: ABI <0.6: Sensitivity 99%, Specificity 68% PLR 3.09 , NLR 0.01ome of amputation: - ABI <0.6: Sensitivity 68%, Specificity 99% $TcPO_2$ <22.5: Sensitivity 100%, Specificity 75% PLR 3.96 , NLR 0.01 (assuming sensitivity of 99%) ABI <0.6: Sensitivity 68%, Specificity 99% PLR 68, NLR 0.32 $TcPO_2$ <22.5: Sensitivity 75%, Specificity 100%		Techniques for measuring ABI and $TcPO_2$ not described in detail Excluded patients who had revascularisation procedures and patients with non-healing ulcers at end of study period – selection bias

					Odds ratio for amputation 2.988 (2.099,4.252)	PLR 75, NLR 0.25 (assuming specificity of 99%)		

* Only ABI and $TcPO_2$ are included from this study. Other parameters were reported in this paper (eg SPP, TBI, TBP) but are not included here as data are not able to be pooled.

Table 3. Event rates for healing and major amputation by study

Source	N (DFU)	Population	Healing n (%)	Annual healing	Major amputation n (%)	Annual major amputation rate
Apelqvist 2011 (12)	1151	DFU	602 (72) (percentage calculated based on 836 patients alive, 310 died with ulcer present)	.....	143 (12)	---
Elgzyri 2014 (13)	478	DFU	217 (45)	54%	76 (16)	19%

Elgzyri 2013 (14)	602	DFU	227 (38)	61%	NS	…
Bunt 1996 (24)	147	Pedal sepsis	NS	…	27 (18)	…
Holstein 1980 (16)	32 (35 limbs)*	DFU	25 (71)	…	10 (29)	…
Wallin 1989 (25)	83 (96 limbs)*	DFU OR gangrene	63 (66)	…	33 (34)	…
Kalani 1999 (18)	50	DFU	20 (40)	40%	4 (8)	8%

Brechow 2013 (19)	678	DFU	NS	…	32 (5)	3%
Faris 1985 (35)	61	DFU OR gangrene	36 (59)	…	NS	…
Gershater 2008 (15)	2511	DFU	1617 (65) healing without minor amputation; 1867 (75) including minor amputations	…	193 (8)	…
Tsai 2013 (17)	97	DFU AND dialysis	NS	…	34 (35)	…
Wang 2016 (11)	ABI group 2376; $TcPO_2$ group 3789.	DFU	NS	NS	NS	NS

Fagher 2018 (21)	236	DFU	55 (23.1) at 3 months	NS	19 (8.1)	NS
Jeon 2017 (36)	137	DFU	60 (55)	NS	5 (3.6%)	NS
Rajagopalan 2018 (23)	564	All diabetic patients with Wagner II and III foot ulcers	470/564=83%	NS	Major amputation (above ankle) 62/564=11%	Not given.

Table 4. Characteristics of Included Studies Evaluating PAD Measures for Healing

Source	**N (DFU)**	**Proportion Men (%)**	**Age (years) mean (SD) or (Range)**	**Population**	**Index test**	**RR**	**PLR**	**NLR**
Apelqvist 2011 (12)	1151	61	75 (40-92)	DFU	Measurable ankle pressure	1.12 (0.80-1.55)	1.02	0.86
Elgzyri 2014 (13)	478	60	74 (IQR 66-80)	DFU	Intermittent claudication	1.25 (1.16-1.36)	1.59	0.81
Elgzyri et al, 2013 (14)	602	60	76 (36-95)	DFU	Ankle pressure >50 mmHg Toe pressure >30 mmHg	1.60 (1.04-2.47) 1.13 (0.96-1.33)	1.08	0.48

							1.12	0.88
Bunt 1996 (24)	147			Pedal sepsis	Palpable pedal pulses Diminished/ absent pedal pulses and $TcPO_2$ >30 mmHg	2.26 (2.05-2.49) 1.69 (1.08-2.64)	NS 1.60	0.65 0.29
Holstein 1980 (16)	32	68		DFU	Toe pressure ≥ 30 mmHg: Ankle pressure ≥ 100 mmHg Skin perfusion pressure ≥ 40 mmHg	2.43 (1.62-3.64) 2.00 (2.00-2.00) 1.88 (1.48-2.39)	NS NS 6.40	0.28 0.40 0.40
Wallin 1989 (25)	83			DFU OR gangrene	Ankle pressure ≥ 70 mmHg Toe pressure ≥20 mmHg Fluorescein toe slope ≥18 units	5.17 (2.08-12.89) 2.65 (1.41-4.97) 6.40 (2.16-18.98)	3.24 2.47 2.47	0.10 0.21 0.09
Kalani 1999 (18)	50	74	61 (12)	DFU	$TcPO_2$ ≥25 mmHg Toe pressure ≥30mmHg Toe pressure ≥45mmHg	NS NS NS	10.03 5.00 2.88	0.16 0.88 0.64
Brechow 2013 (19)	678		64 (11)	DFU	ABI >0.9 and <1.3	2.02 (1.40-2.91)	2.61	0.92

Faris 1985 (20)	61		72 (38-86)	DFU or gangrene	Skin perfusion pressure ≥40mmHg	NS	4.86	0.03
Gershater 2008 (15)	2511	59	68 (15)	DFU	Ankle pressure ≥80mmHg Ankle pressure ≥50mmHg Toe pressure ≥45mmHg Toe pressure ≥30mmHg	2.67 (2.41-2.97) 3.31 (2.71-4.05) 2.86 (2.62-3.12) 1.85 (1.61-2.14)	2.52 1.46 4.30 1.28	0.24 0.15 0.25 0.33
Wang 2016 (11)	ABI group 2376; TcPO2 group 3789.	ABI group - pooled mean 59.6; TcPO2 group – pooled mean 70	ABI group - pooled mean 60.7; TcPO2 group – pooled mean 69.67	DFU	ABI ≥0.8 $TcPO_2$ ≥30mmHg	Diagnostic odds ratio for healing 1.02 (0.40-2.65) Diagnostic odds ratio for healing 15.81 (3.36-74.45)	1.00 5.14	1.00 0.33
Fagher 2018 (21)	236	69.9	76 (69-82)	DFU	$TcPO_2$ ≥25mmHg	2.98 (1.13-7.86)	1.21	0.33
Jeon 2017 (22)	137	58	61 (13)	DFU	ABI ≥ 0.9	2.92 (1.76-4.84)	2.58	0.29
Rajagopalan 2018 (23)	564	380/564=67.4 % Men	Mean age 58.23±10.11 years	All diabetic patients with	ABI >0.9	Sensitivity 41.5% Specificity 97%	13.83	0.6

				Wagner II and III foot ulcers	$TcPO_2$ >40mmHg	Sensitivity 43.6% Specificity 84%	2.73	0.67

Note: *Definition of PAD using same reference test varied; see Table 4; †In combination with ABPI <0.9; DM, diabetes mellitus; SD, standard deviation; PLR positive likelihood ratio; NLR, negative likelihood ratio; DUS, duplex ultrasound; DSA, digital subtraction angiography; dABPI, doppler ankle brachial pressure index; oABPI, oscillometric ankle brachial pressure index; TBI, toe brachial index; PN+, with peripheral neuropathy; PN-, without peripheral neuropathy; NS, not stated; NA, not applicable (cannot be calculated).

Table 5. Characteristics of Included Studies Evaluating PAD Measures for Major Amputation

Source	**N (DFU)**	**Proportion Men, %**	**Age (years), mean (SD) or (Range)**	**Population**	**Index test**	**RR**	**PLR**	**NLR**
Wallin 1989 (25)	83			DFU OR gangrene	Ankle pressure < 70 mmHg	4.53 (2.22-9.26)	4.28	0.41
					Toe pressure < 20 mmHg	3.48 (1.65-7.32)	3.18	0.49
					Fluorescein toe slope <18 units	3.69 (1.99-6.86)	4.04	0.49
Brechow 2013 (19)	678		64 (11)	DFU	ABI<0.5 or ankle pressure <50mmHg	25.00 (13.5-41.92)	8.24	0.14
Gershater 2008	2511	59	68 (15)	DFU	Ankle pressure <80mmHg	2.26 (1.71-2.97)	1.89	0.77

(15)					Ankle pressure <50mmHg Toe pressure <45mmHg Toe pressure <30mmHg	1.29 (0.92-1.80) 2.98 (2.28-3.91) 3.24 (2.48-4.24)	1.25 2.05 2.64	0.95 0.62 0.71
Tsai 2013 (17)	97	55	65 (3)	DFU AND dialysis	Poor monophasic waveform or absence of flow in below knee vessels	7.61 (NS)	2.18	0.20
Wang 2016 (11)	ABI group 2376; TcPO2 group 3789.	ABI group - pooled mean 59.6; TcPO2 group – pooled mean 70	ABI group - pooled mean 60.7; TcPO2 group – pooled mean 69.67	DFU	ABI <0.8 $TcPO_2$ <30mmHg	Diagnostic odds ratio 2.89 (1.65-5.05) Diagnostic odds ratio 4.14 (2.98-5.76)	1.93 1.79	0.66 0.43
Fagher 2018 (21)	236	69.9	76 (69-82)	DFU	$TcPO_2$ ≤25mmHg	5.53 (2.36-12.97)	3.41	0.51
Jeon 2017 (22)	137	58	61 (13)	DFU	ABI < 0.9	3.10 (1.93-4.99)	3.45	0.39
Rajagopalan 2018 (23)	564	380/564=67.4% Men	Mean age 58.23±10.11 years	DFU	ABI <0.6 $TcPO_2$ <22.5	Sensitivity 68%, Specificity 99% Sensitivity 75%, Specificity 100%	68 68	0.32 0.25

Note: *Definition of PAD using same reference test varied.

†In combination with ABPI <0.9; DM indicates diabetes mellitus; SD, standard deviation; PLR positive likelihood ratio; NLR, negative likelihood ratio; DUS, duplex ultrasound; DSA, digital subtraction angiography; dABPI, doppler ankle brachial pressure index; oABPI, oscillometric ankle brachial pressure index; TBI, toe brachial index; PN+, with peripheral neuropathy; PN-, without peripheral neuropathy; NS, not stated; NA, not applicable (cannot be calculated).